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Original Article

Phase advancing human circadian rhythms with morning bright light, afternoon melatonin, and gradually shifted sleep: can we reduce morning bright-light duration?

Stephanie J. Crowley *, Charmane I. Eastman

Biological Rhythms Research Laboratory, Department of Behavioral Sciences, Rush University Medical Center, 1645 West Jackson Blvd. Suite 425, Chicago, IL 60612, USA

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ABSTRACT

Objective: Efficient treatments to phase-advance human circadian rhythms are needed to attenuate circadian misalignment and the associated negative health outcomes that accompany early-morning shift work, early school start times, jet lag, and delayed sleep phase disorder. This study compared three morning bright-light exposure patterns from a single light box (to mimic home treatment) in combination with afternoon melatonin.

Methods: Fifty adults (27 males) aged 25.9 ± 5.1 years participated. Sleep/dark was advanced 1 h/day for three treatment days. Participants took 0.5 mg of melatonin 5 h before the baseline bedtime on treatment day 1, and an hour earlier each treatment day. They were exposed to one of three bright-light (~5000 lux) patterns upon waking each morning: four 30-min exposures separated by 30 min of room light (2-h group), four 15-min exposures separated by 45 min of room light (1-h group), and one 30-min exposure (0.5-h group). Dim-light melatonin onsets (DLMOs) before and after treatment determined the phase advance.

Results: Compared to the 2-h group (phase shift = 2.4 ± 0.8 h), smaller phase-advance shifts were seen in the 1-h (1.7 ± 0.7 h) and 0.5-h (1.8 ± 0.8 h) groups. The 2-h pattern produced the largest phase advance; however, the single 30-min bright-light exposure was as effective as 1 h of bright light spread over 3.25 h, and it produced 75% of the phase shift observed with 2 h of bright light.

Conclusions: A 30-min morning bright-light exposure with afternoon melatonin is an efficient treatment to phase-advance human circadian rhythms.

1. Introduction

Misalignment between the circadian clock and 24-h rhythmic behaviors such as sleep/wake and fasting/feeding ("circadian misalignment") is associated with sleep disruption, excessive sleepiness, and cognitive decrements during wake, and gastrointestinal problems [1–12]. The most recognized cause of circadian misalignment is jet lag after crossing multiple time zones, although night-shift work and early school or work times are other situations in which individuals can experience circadian misalignment. In laboratory studies that experimentally imposed severe acute circadian misalignment, healthy participants showed adverse metabolic responses that are risk factors for cardiovascular disease and type 2 diabetes [1,8,9]. When experienced chronically like in night-shift work, circadian misalignment increases the risk of a number of diseases, including cancer [13–18].

Appropriately timed sleep (dark), light, and exogenous melatonin can phase-shift circadian rhythms, and therefore they can be used to reduce the degree of circadian misalignment and attenuate risks of negative health and daily functioning outcomes [7,11,12]. The direction and magnitude of the shift is predicted by phase response curves (PRCs) [19–29]. Advancing the system (shifting it earlier) is more difficult and typically takes longer than delaying (shifting it later). This may be in part because most humans have an endogenous period that is slightly longer than 24 h [30–34], which favors the ability to delay. Of note, however, mice also have more difficulty advancing despite their average free-running period being <24 h [35]. Our laboratory has focused on testing methods to advance rhythms to attenuate circadian misalignment, which could be utilized by travelers flying east, shift workers who need to wake early for early-morning shifts or who want to take all of their daily sleep

Abbreviations: DLMO, dim-light melatonin onset; PRC, phase response curve; DSPD, delayed sleep phase disorder; SAD, seasonal affective disorder; h, hour; min, minute; BMI, body mass index; PSQI, Pittsburgh Sleep Quality Index; SSS, Stanford Sleepiness Scale.

* Corresponding author. Biological Rhythms Research Laboratory, Department of Behavioral Sciences, Rush University Medical Center, 1645 West Jackson Blvd. Suite 425, Chicago, IL 60612, USA. Tel.: +312 563 4783; fax: +312 563 4900.
E-mail address: stephanie_j_crowley@rush.edu (S.J. Crowley).

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before a night shift, and extreme night owls or patients with delayed sleep phase disorder (DSPD) who struggle to wake up for work or school. Indeed, the most recent American Academy of Sleep Medicine Practice parameters for treatment of circadian rhythm sleep disorders [36] indicated (guideline) timed light exposure and timed melatonin administration for shift work disorder and DSPD. In a gradual sleep/dark shift paradigm, we have examined phase advances in response to afternoon melatonin alone [37], morning bright light alone [38–40], as well as the combination of afternoon melatonin and morning bright light [41] in healthy young adults. The latter combination of afternoon melatonin and morning bright-light exposure produced the largest phase-advance shifts (~2.5 h) over 3 days of treatment.

One of the criticisms of bright-light treatment, however, is that it is time consuming, which could impact compliance to treatment. Little data exist on compliance to the use of bright light (either sunlight or light boxes) for reducing circadian misalignment, although a few reports describing light therapy for seasonal affective disorder (SAD) suggest that compliance rates to using bright-light boxes are mediocre in this particular group of patients. Michalak and colleagues [42] reported that, over a 4-week intervention, mean adherence to the prescribed bright-light treatment was 59%. Others have reported rates of long-term use of prescribed bright-light therapy for SAD ranging between 11% and 42% [43,44]. Therefore, identifying an effective and efficient duration of bright-light treatment that patients can realistically follow is warranted.

Many studies of phase shifting designed for practical purposes used long durations (≥3 h) of continuous bright-light exposures [38,45–54]; however, intermittent bright-light exposure is likely more feasible and it mimics real-life treatment patterns compared to continuous light exposure [55,56]. For this reason, we often utilize intermittent bright light in our studies [57–59]. Furthermore, previous studies from our laboratory [38] and others [60,61] showed that intermittent bright-light patterns can be almost as effective as continuous exposure producing about 60–90% of the phase shift obtained with continuous exposure. These data may suggest that the total time that the light is on may not be as important as the amount of time light exposure spans the appropriate portion of the PRC to light. Alternatively, or in addition, the beginning of a bright-light exposure may be the most effective in eliciting a phase-resetting response due to light adaptation [62].

While using a sleep schedule that was advanced by 1 h/day for 3 days, we previously tested the combination of intermittent morning bright light and afternoon melatonin [41] to produce a phase advance while maintaining circadian alignment. The purpose of the current study was to identify whether there was a more efficient bright-light treatment that could be implemented in combination with 0.5 mg of exogenous melatonin to phase-advance rhythms. The light pattern in the previous study [41] was intermittent such that the bright-light box was turned on four times for 30 min with 30 min of normal room lighting in between. Therefore, the total bright-light exposure was 2 h, but the total treatment time was spread over 3.5 h. Using this "2-h" group as a comparison group, the aims of this study were to examine whether phase-advance shifts were smaller when total bright-light treatment duration was shortened using the following strategies: (1) reducing the duration of the intermittent bright-light exposures from 30 to 15 min ("1-h" group) and (2) reducing the number of bright-light exposures from four to one 30-min exposure ("0.5 h" group). Two additional groups of participants completed the study, and they were compared to the historical comparison group.

2. Methods

2.1. Participants

Data from 50 participants (27 males) aged 18–40 years (mean = 25.9 ± 5.1 years) were included in this analysis. The 2-h group included 16 participants (10 males), the 1-h group included 17 participants (nine males), and the 0.5-h group included 17 participants (eight males). Age, sex distribution, morningness/eveningness, and body mass index (BMI) did not differ among the three bright-light groups. Morningness-eveningness was measured using the Horne-Östberg questionnaire [63]; 32 participants were intermediate types, 10 were moderate morning types, six were moderate evening types, one was a definite morning type, and one was a definite evening type (mean = 52.2, SD = 8.6). BMI was <30 kg/m^2 (mean ± SD = 23.4 ± 2.8), and they weighed between 47 and 96 kg (mean ± SD = 68.5 ± 10.5 kg). The majority of participants (66%) reported their race as White/Caucasian (12% Black/African American, 10% Asian, 6% more than one race, and 6% other); race distribution did not differ among groups. Inclusion/exclusion criteria and procedures for all groups were similar, and they are described together below.

All participants were free of medical and psychiatric disorders, as assessed by in-person interviews, the Minnesota Multiphasic Personality Inventory-2 (MMPI-2), and part of a health questionnaire [64]. Participants reported not taking any prescription medications, except for five women who were taking oral contraceptives. Participants reported no more than moderate alcohol (≤2 drinks per day) and caffeine (<500 mg per day) intake, and they were non-smokers. The inclusion criteria included habitual sleep duration between 6.5 and 9 h per night, habitual bedtimes between 23:00 and 02:00, and habitual wake times between 07:00 and 10:00. Participants reported no sleep problems over the proximal month of enrollment as assessed by a Pittsburgh Sleep Quality Index (PSQI) [65] score of ≤5, and no problems with excessive daytime sleepiness as assessed by an Epworth Sleepiness Scale [66] score of <10. Participants reported not working night shifts during the 2 months before the start of the study or crossing >3 time zones in the month before beginning the study.

The Rush University Medical Center Institutional Review Board approved the study protocols, and, therefore, the study was performed in accordance with the ethical standards outlined in the 1964 Declaration of Helsinki. Each participant gave written informed consent.

2.2. Procedures

2.2.1. Experimental protocol

Participants completed the 14-day protocol illustrated in Fig. 1. Each participant was given a fixed sleep schedule to follow at home during baseline days (1–6 and 8–11) and were provided 8 h of time in bed. The sleep schedule assigned to each participant was based on their reported average bedtime and wake time before starting the study. Assigned baseline bedtimes ranged from 23:00 to 02:00 (mean = 00:10, SD = 56 min), and thus wake time ranged from 07:00 to 10:00 (mean = 08:10, SD = 56 min). Each baseline morning, participants were required to go outside for at least 10 min during the second hour after waking for daylight exposure. The fixed sleep schedule and morning light was designed to stabilize the circadian phase and ensure that participants were not sleep deprived before the phase-advancing treatment in the laboratory. Participants slept at home on days 1–6 and 8–11; on the other days, they slept in private temperature-controlled bedrooms in the laboratory. Participants lived in the laboratory from days 12 through 15. Wake times in the laboratory were gradually advanced by 1 h/day over the three treatment days (days 12, 13, and 14). Bedtimes were also advanced by 1 h/day, except in the 2-h group. Participants in the 2-h group were put to bed at their baseline bedtime on the first treatment day instead of 1 h earlier. Then their bedtime shifted by 2 h relative to baseline on the second treatment day (day 13), and by 3 h relative to baseline on the third treatment day (day 14). On the second and third treatment days, the sleep schedule among the three

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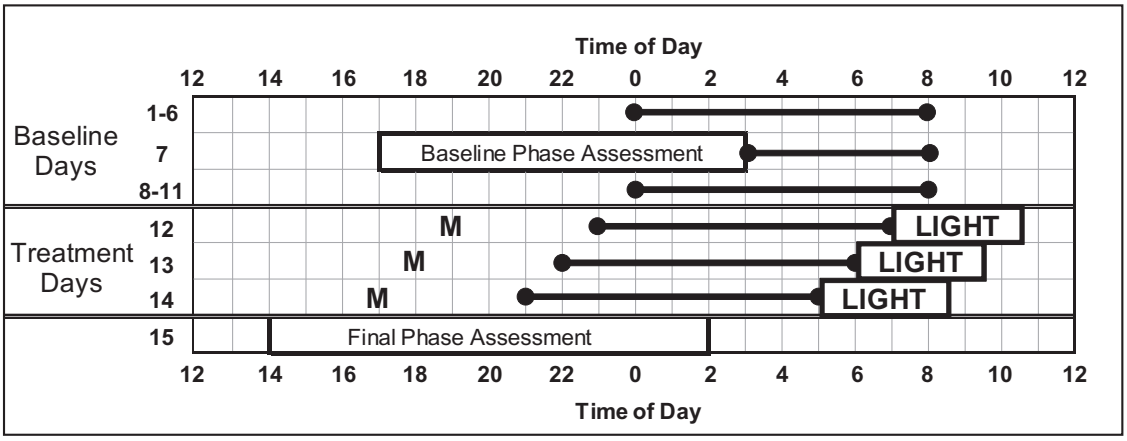

Fig. 1. Protocol diagram. The 2-week protocol included baseline days (1–11) and treatment days (12–14). Days 12, 13, and 14 are also referred to as treatment days 1, 2, and 3, respectively, in the text. The horizontal lines anchored with circles illustrate scheduled sleep times. A participant with a baseline bedtime of midnight (0) and baseline wake time of 08:00 is shown as an example. Baseline sleep schedules always allowed for 8 h of time in bed, but bed and wake times varied among participants as they were based on self-reported sleep times before beginning the study. The sleep schedule was gradually advanced on days 12, 13, and 14. Participants ingested 0.5 mg of melatonin (M) 5 h before their baseline bedtime on the first treatment day and then 1 h earlier on each subsequent treatment day. Bright light (~5000 lux) from a single light box was administered within 5 min of waking on each of the three treatment days. On days 7 and 15, participants completed a circadian phase assessment to determine the dim-light melatonin onset (DLMO).

treatment groups were the same relative to their baseline sleep schedules. The gradual advance of sleep/dark over the three treatment days was designed to maintain alignment between sleep and circadian rhythms during the treatment and to facilitate a phase-advance shift [38,67].

Participants were permitted to consume caffeine (up to 100 mg) during the first 3 h of wake on baseline days 1–3. A maximum of two standard alcoholic drinks were permitted on Fridays and Saturdays (days 1, 2, 8, and 9) of the study. Participants were tested for alcohol using a Breathalyzer before each phase assessment. Non-steroidal anti-inflammatory drugs were not permitted during the entire study, as these drugs suppress melatonin [68]. Recreational drugs and nicotine were prohibited throughout the study.

The study ran throughout the year (January through December), and therefore it occurred during all seasons. The number of subjects participating in each season (defined as spring, March 1–May 31; summer, June 1–August 31; fall, September 1–November 30; and winter, December 1–February 28) did not differ among groups (X^2 (6) = 4.89, p = 0.56).

2.2.2. Bright light

Soon after waking on the three treatment days (12, 13, and 14 in Fig. 1), the participants sat at a desk in their private bedroom in front of a single bright-light box (54 × 54 cm diffuser screen; Enviro-Med, Vancouver, WA, USA) approximately 40 cm from their eyes. The light box contained four 54-cm, 40-W cool white fluorescent horizontal lamps (PL-L 40W/41/RS/IS, 4100K; Philips).

Figure 2 illustrates the three light patterns we compared in this between-subject design. In each group, the light box was turned on within 5 min of the scheduled wake time. In the "2-h" group, participants received four 30-min exposures of bright light with 30 min of room light in between. To test whether reducing the duration of the intermittent bright-light exposures affects phase advances, a second group of participants (the "1-h" group) received four 15-min exposures of bright light with 45 min of room light in between. To test whether reducing the duration of bright light by reducing the number of exposures affect phase advances, a third group (the "0.5-h" group) received one 30-min bright-light exposure only. Light intensity measured with a Minolta TL1 illuminance meter (KONICA MINOLTA, INC. Tokyo, Japan) ranged from 3500 to 6880 lux at the angle of gaze (mean = 4829, SD = 831 lux). A similar illuminance range was measured in each group: 0.5-h group: 3500–6440 lux; 1-h group: 3520–6490 lux; and 2-h group: 3510–6880 lux. The illuminance meter came from the manufacturer calibrated; we did not calibrate the meter. While awake and while the bright-light box was off, one ceiling fixture with fluorescent tubes (4100 K) was on and dimmed to the lowest setting in the bedroom. The light intensity in the angle of gaze averaged 18.6 ± 16.6 lux and ranged from 4.1 to 93.9 lux. The ceiling lights were controlled by staff members in a separate control room. The angle of gaze was not controlled during the study because this is not how bright-light treatment is delivered in the home.

2.2.3. Exogenous melatonin

All participants were given 0.5 mg of melatonin (Ecological Formulas, Cardiovascular Research Ltd., Concord, CA, USA) on each treatment day. The pill administration was double-blind; research staff administered the pill and were told that it was melatonin or placebo. Participants did not eat or drink anything 2 h before until 30 min after ingesting the pills. Participants provided saliva samples 1 and 2 h after pill ingestion to confirm that melatonin pills were correctly administered. These samples were later assayed for melatonin concentration. No melatonin doses were missed. We chose a small dose of melatonin (0.5 mg) to reduce the risk of evening sleepiness [37]. The half-life of exogenous melatonin ranges from about 45 to 60 min [23,69–71]. Based on previous findings

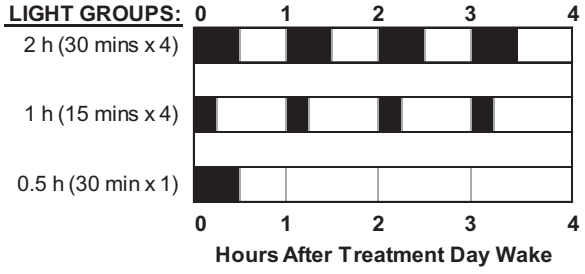

Fig. 2. Morning bright-light patterns (~5000 lux) for each group. Dark bars indicate when lights were on relative to wake time. Between bright-light pulses, participants remained in room light (~20 lux at the angle of gaze).

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[23,69–71], the peak melatonin values in the current study likely occurred approximately 1–2 h after ingestion.

On the first treatment day, we administered the 0.5-mg dose of melatonin 5 h before baseline bedtime (9 h before the baseline mid-sleep time), which targets the phase-advance portion of the 0.5-mg PRC [25]. The timing of the pills was advanced by 1 h each day because theoretically the circadian system is advancing each day; timing the dose earlier each day increased the likelihood of exogenous melatonin falling near the optimal time for phase advances according to the 0.5-mg melatonin PRC. We did not administer melatonin according to body weight because it is not sold to consumers based on this. Based on the weight (in kg) of the participants, the dose averaged 0.007 ± 0.001 mg/kg, and it ranged from 0.005 to 0.011 mg/kg.

2.2.4. Dim-light melatonin onset phase assessments

Endogenous salivary melatonin concentration was measured from approximately 2 mL of saliva collected every 30 min using Salivettes (Starstedt, Nümbrecht, Germany). Saliva collection for the baseline phase assessment began 7 h before and ended 3 h after the assigned baseline bedtime. Saliva collection for the final phase assessment began 10 h before and ended 2 h after the baseline bedtime. Participants remained awake in dim light (<5 lux), sitting in comfortable recliners. Each sample was immediately centrifuged to extract saliva and then frozen. Saliva samples were later radioimmunoassayed (RIA) for melatonin concentration (Pharmasan Labs, Inc., Osceola, WI, USA). An individual's samples were analyzed in the same batch. The sensitivity of the assay was between 0.7 and 1 pg/ml. The intra-assay coefficient of variation for low daytime levels of salivary melatonin was 12%. The inter-assay coefficients of variation for low daytime levels of salivary melatonin ranged from 13.2% to 15.9%.

2.2.5. Sleep and ambient light monitoring

Participants completed daily sleep logs to record bedtime, estimated sleep onset time, nighttime awakenings > 5 min, final wake time, and the time they got out of bed. Participants wore actigraphs (Actiwatch-L, Philips Respironics, Inc., Bend, OR, USA) on their wrist. They wore another Actiwatch-L (without the wristband) on a cord around their necks as a medallion to measure compliance to the 10-min outdoor morning light requirement during baseline. When sleeping at home, participants called the laboratory's time-stamped voice mail system at bedtime and wake time. Activity and light data with the daily logs were reviewed with participants every 2–3 days at the laboratory to verify compliance.

2.2.6. Subjective symptoms

Within 30 min of the scheduled bedtime on baseline and treatment days, participants completed the Columbia Jet Lag Scale [72] to rate how they felt all day. This nine-item scale asked participants to rate how much they were bothered by sleepiness, fatigue, decreased daytime alertness, trouble concentrating or thinking clearly, lethargy/sluggish feeling, light-headed/dizziness, feelings of weakness, physical clumsiness, and trouble with memory on a scale of 0 (not at all) to 4 (extremely). A total sum score was computed with a possible range of 0–36. Participants also completed the Stanford Sleepiness Scale (SSS) [73] four or five times throughout the day during baseline and treatment days. Participants completed the SSS 15–30 min after waking, 15–60 min before bedtime, and two to three other times evenly spaced throughout the day. The SSS is a seven-point Likert scale with the following anchored descriptions: 1 = feeling active and vital; alert, wide awake; 2 = functioning at high level, but not at peak; able to concentrate; 3 = relaxed; awake; not at full alertness; responsive; 4 = a little foggy; not at peak; let down; 5 = fogginess; beginning to lose interest in remaining awake; slowed down; 6 = sleepiness; prefer to be lying down; fighting sleep; woozy; and 7 = almost in reverie; sleep onset soon; must struggle to remain awake.

2.3. Data and statistical analyses

2.3.1Dim-light melatonin onset.

Raw melatonin curves were smoothed using a locally weighted least squares (LOWESS) curve generated using Prism software (GraphPad, Inc., San Diego, CA, USA). The threshold for each phase assessment was the average of the five lowest continuous daytime values from the beginning of the phase assessment plus 15% of the average of the five highest continuous values. Baseline and final phase assessment thresholds for an individual were averaged. The dim-light melatonin onsets (DLMOs) were the clock times at which the smoothed curves crossed this averaged threshold. We have implemented this method for calculating the DLMO previously [40,59,74–77] because it takes into account differences in the amplitude of the absolute levels of melatonin, which vary substantially between participants. In contrast to the DLMO20% (eg, Ref [78].) or DLMO25% (eg, Ref [79].) method, this threshold is typically lower on a melatonin profile (ie, closer to the actual time of melatonin secretion onset), but above the low daytime background level of melatonin. The phase shift is the baseline DLMO minus the final DLMO; by convention, phase advances are positive numbers and phase delays are negative numbers.

To determine whether the DLMO phase advance differed among the three bright-light groups, a 2 (time: baseline vs. final) × 3 (group: 2 vs. 1 vs. 0.5 h) repeated measures omnibus analysis of variance (ANOVA) was computed. To determine whether DLMO phase advances differed after reducing the duration of the light exposures from 30 to 15 min, a 2 (time: baseline vs. final) × 2 (bright-light group: 2 vs. 1 h) repeated measures ANOVA was computed. To test whether DLMO phase advances differed after reducing the number of light exposures from four to one, a 2 (time: baseline vs. final) × 2 (bright-light group: 2 vs. 0.5 h) repeated measures ANOVA was computed. When the assumption of sphericity was violated, Greenhouse–Geisser corrections were used, although the original degrees of freedom are reported here.

2.3.2. Sleep

Wrist activity data were analyzed using the Actiware 5 software (version 5.59, Respironics, Inc., Bend, OR, USA) to estimate sleep/wake (medium threshold; immobile minutes algorithm). Each sleep episode was inspected within a rest interval beginning with the participants' reported bedtime and ending with their reported wake time on their daily sleep log. The following variables were derived: sleep-onset time, wake time, and total sleep time. To examine whether sleep timing or duration differed among the three groups, 3 (bright-light group) × 4 (time: baseline, treatment days 1, 2, and 3) repeated measures ANOVAs were computed. When the assumption of sphericity was violated, Greenhouse-Geisser corrections were used, although the original degrees of freedom are reported here.

2.3.3. Subjective symptoms

Subjective symptoms were derived from the Columbia Jet Lag Scale and SSS. Ratings on days 2–6 were averaged to define baseline and were compared to treatment day 3 (from waking for the second light treatment on day 13 until bedtime on day 14), because this day followed one night of similar time in bed among the groups. A 2 (time: baseline vs. treatment day 3) × 3 (bright-light group) repeated measures ANOVA was used to determine whether symptoms near the end of treatment became worse, and whether the change in symptoms differed among the bright-light groups.

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Table 1
Phase shifts and circadian phase (mean ± SD) marked by the dim-light melatonin onset (DLMO) for all bright-light groups.

	Bright-light group		
	2 h (30 min × 4)	1 h (15 min × 4)	0.5 h (30 min × 1)
N	16 (10 M, 6 F)	17 (9 M, 8 F)	17 (8 M, 9 F)
DLMO phase advance (h)	2.4 ± 0.8	1.7 ± 0.7**	1.8 ± 0.8*
Baseline DLMO	21:25 ± 01:17	21:36 ± 01:20	21:39 ± 01:30
Final DLMO	19:00 ± 00:58	19:56 ± 01:22	19:52 ± 01:30
Baseline DLMO to baseline bedtime (h)	2.6 ± 1.2	2.7 ± 0.7	2.3 ± 1.2
Final DLMO to treatment day 3 bedtime (h)	2.1 ± 0.7	1.4 ± 0.6	1.2 ± 1.0
Administration times (treatment day 1)			
Melatonin pill to baseline DLMO (h)	2.4 ± 1.2	2.3 ± 0.7	2.6 ± 1.1
Baseline DLMO to start of bright light (h)	9.7 ± 1.2	9.7 ± 0.7	9.4 ± 1.1

* $p < 0.05$, **$p < 0.01$ compared to the 2-h group.

3. Results

3.1. DLMO phase advance

Table 1 shows the sex distribution and sample size for each group and the magnitude of the phase shifts in the DLMO. All three groups phase-advanced from the baseline to the final phase assessment (time: $F(1.47) = 336.9$, $p < 0.001$). In comparison to the 2-h group, however, smaller phase-advance shifts were seen in the 1-h and 0.5-h groups (time × group: $F(2.47) = 4.6$, $p = 0.02$). The 1-h and 0.5-h groups showed similar phase-advance shifts (see Table 1 and Fig. 3A).

Figure 3B illustrates the average baseline and final DLMOs for the 2-h and 1-h groups. In combination with a gradually advancing sleep/dark schedule and afternoon melatonin, reducing the duration of the four morning light exposures from 30 to 15 min decreased the average phase-advance shift by 42 min. There was a significant time ($F(1.31) = 260.9$, $p < 0.001$) and time-by-group interaction ($F(1.31) = 8.43$, $p = 0.007$).

Figure 3C illustrates the baseline and final DLMOs for the 2-h and 0.5-h groups. When the number of 30-min bright-light exposures was reduced from four to one, the phase-advance shift decreased by an average of 36 min. There was a significant time ($F(1.31) = 234.6$, $p < 0.001$) and time-by-group interaction ($F(1.31) = 5.35$, $p = 0.028$).

Baseline DLMOs were similar among the three bright-light groups, and the timing of morning bright light and 0.5 mg of melatonin on the first treatment day in the laboratory (day 12) relative to baseline DLMO did not differ among groups (see Table 1). Bright light started 6.8–11.9 h after baseline DLMO. As expected based on properties of the light PRC, bright light that started in the earlier part of this range showed larger phase-advance shifts compared to those that started later in this range (Fig. 4). A significant negative linear association was seen between the phase shift and light start time in the 2-h group ($r = -0.83$, $p < 0.001$), the 1-h group ($r = -0.62$, $p = 0.008$), and the 0.5-h group ($r = -0.50$, $p = 0.041$). The melatonin pill was always given 12 h before the scheduled wake time and the start of light treatment; therefore, the correlation coefficients showing the association between the phase-advance shift and the timing of the melatonin pill relative to DLMO are the same.

3.2. Sleep

Actigraphic estimates of sleep during baseline and during treatment days for each bright-light group are included in Table 2. Sleep timing and duration did not differ among groups during baseline or on treatment days 2 and 3. The 2-h group had 7 h in bed on treatment day 1, because their bedtime was not advanced on that day, so their total sleep time was about 1 h less than for the other two groups who had 8 h in bed.

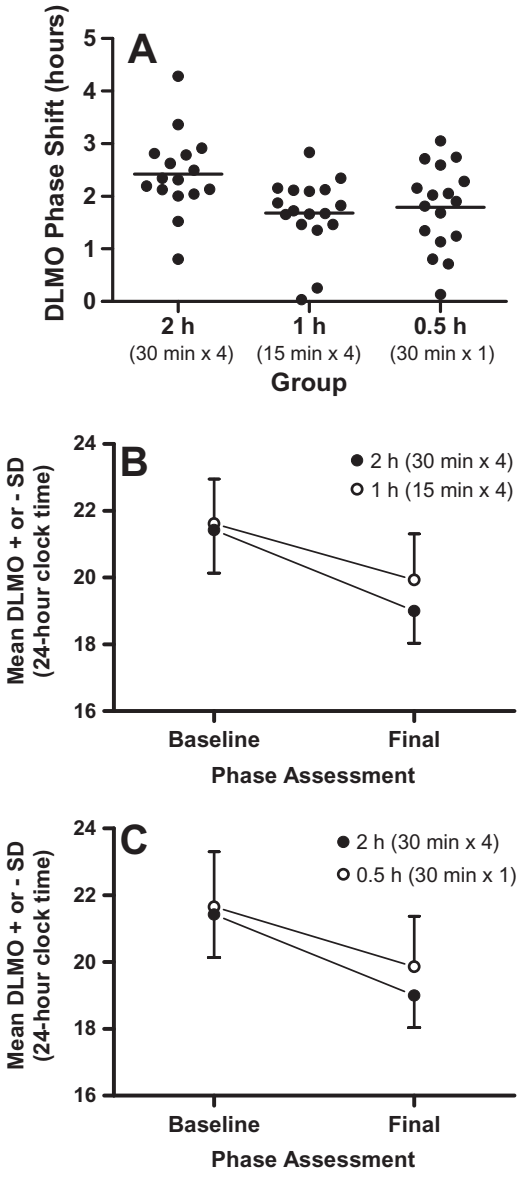

Fig. 3. Phase shifts to intermittent morning bright light plus afternoon melatonin. (A) Black circles illustrate the phase-advance shifts for each individual, and horizontal lines illustrate mean phase shifts for each bright-light group. (B) Mean DLMO at baseline and final assessments for the 2-h group in comparison to the 1-h group, which differed in bright-light exposure duration (30 vs. 15 min). (C) Mean DLMO at baseline and final assessments for the 2-h group in comparison to the 0.5-h group, which differed in light exposure number (four vs. one 30-min light exposure). The phase advance was significantly larger in the 2-h group.

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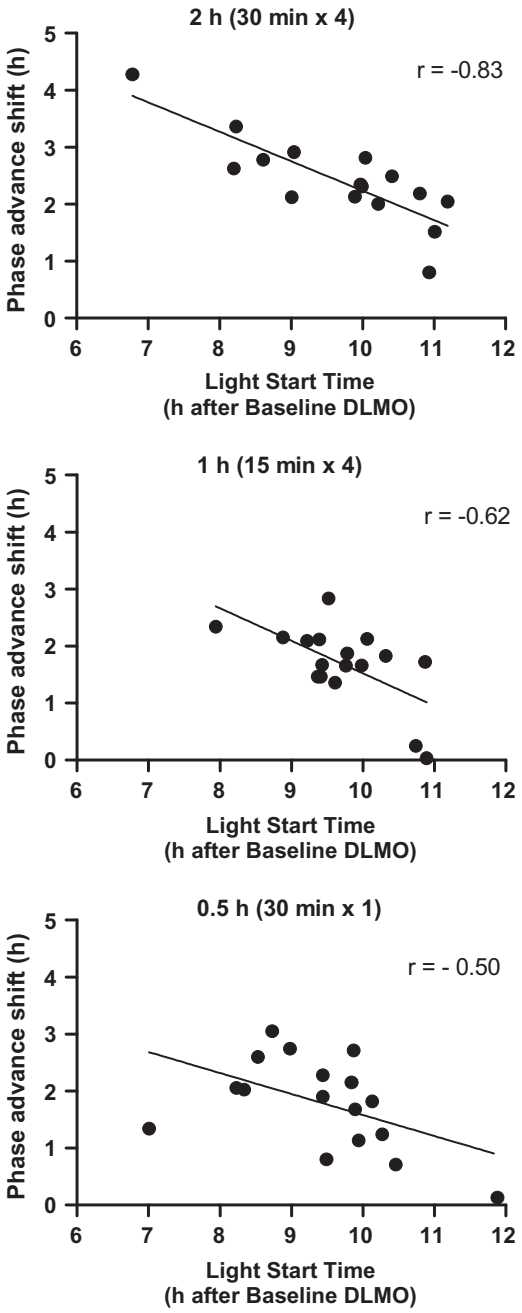

Fig. 4. Scatter plots showing the association between the time of the morning bright light (relative to the DLMO) and the magnitude of the phase advance. Light start time is the interval between the baseline DLMO and the start of morning light exposure on the first treatment morning. A linear regression line (solid line) was fit separately for each group.

3.3. Subjective symptoms

Figure 5 shows that jet lag symptoms measured from the Columbia Jet Lag Scale showed a small increase compared to baseline on treatment day 3 (from wake on day 13 in Fig. 1 to right before bed on day 14) for all bright-light groups compared to baseline (time: $F(1.45) = 9.7$, $p = 0.003$); scores for all three groups increased by about two points on this scale, which has a maximum value of 36. Despite smaller phase-advance shifts in the 1-h and 0.5-h groups in comparison to the 2-h group, jet lag symptoms did not differ among the groups. Participants did not rate their sleepiness differently on treatment day 3 compared to baseline, and subjective sleepiness ratings did not differ among the three bright-light groups.

Table 2
Mean ± SD actigraphic estimates of sleep-onset time, wake time, and total sleep time during baseline (days 1–6 and 8–11) and the three treatment days (days 12, 13, and 14) for each bright-light group.

	Bright-light group		
	2 h (30 min × 4)	1 h (15 min × 4)	0.5 h (30 min × 1)
Baseline:			
Sleep-onset time	00:16 ± 0:48	00:31 ± 1:03	00:17 ± 1:04
Wake time	7:55 + 0:43	8:08 ± 1:01	7:54 + 0:59
Total sleep time (h)	6.9 ± 0.4	7.0 ± 0.37	7.0 ± 0.2
Treatment day 1:			
Sleep-onset time	00:10 ± 0:44	23:27 ± 1:05	23:10 ± 1:03*
Wake time	6:54 ± 0:45	7:13 ± 1:02	6:54 ± 0:58
Total sleep time (h)	6.1 ± 0.5	7.1 ± 0.4*	7.2 ± 0.4*
Treatment day 2:			
Sleep-onset time	22:12 ± 0:45	22:24 ± 1:05	22:13 ± 1:04
Wake time	5:58 ± 0:46	6:11 ± 1:03	5:48 ± 0:58
Total sleep time (h)	7.0 ± 0.5	7.1 ± 0.4	7.0 ± 0.5
Treatment day 3:			
Sleep-onset time	21:13 ± 0:45	21:29 ± 1:06	21:15 ± 1:04
Wake time	4:51 ± 0:47	5:11 ± 1:01	4:57 ± 0:58
Total sleep time (h)	6.8 ± 0.7	7.1 ± 0.5	7.0 ± 0.3

* $p < 0.05$ compared to the 2-h group.
4 (time) × 3 (bright-light group) repeated measures ANOVA:
Sleep-onset time (time: $F(3.141) = 6281.5$, $p < 0.001$; time × group: $F(6.141) = 91.0$, $p < 0.001$).
Wake time (time: $F(3.141) = 2682.6$, $p < 0.001$).
Total sleep time (time: $F(3.141) = 5.0$, $p = 0.002$; time × group: $F(6.141) = 17.7$, $p < 0.001$).

4. Discussion

This study is part of a series of studies in our laboratory aimed at testing methods to phase-advance human circadian rhythms using afternoon melatonin and/or morning bright light from a single light box [37–41]. We combined these zeitgebers with a gradually advancing sleep/dark schedule rather than an abrupt advance of the sleep schedule to limit the degree of circadian misalignment between the internal circadian system and sleep/wake during treatment. This method is designed to advance circadian rhythms before flying east to reduce or eliminate jet lag or to advance the rhythms of people who want to have an earlier schedule for other reasons, such as shift workers on early-morning shifts or extreme night owls and people with DSPD who want to be able to fall asleep and wake up earlier.

In this report, we compared three different morning light patterns combined with a low dose of afternoon melatonin (0.5 mg)

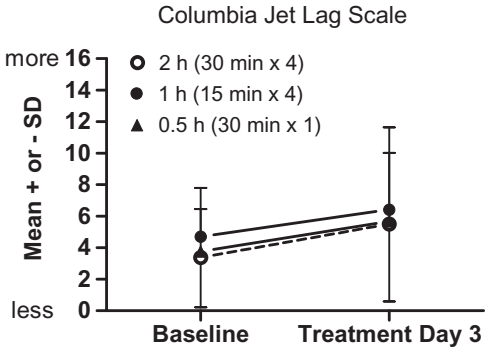

Fig. 5. Mean subjective ratings of jet lag at baseline (days 2–6) and treatment day 3 (from wake time on day 13 to bedtime on day 14) for the three bright-light groups. The 2-h group is differentiated by an open symbol and dotted line to more easily compare it to the 1-h (closed circle) and 0.5-h (closed triangle) groups. There was a slight increase in subjective jet lag (the maximum score is 36), but there were no differences among the groups.

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and a sleep/dark schedule that was advanced by 1 h/day for 3 days. The group that received the longest duration of morning bright light each day (2-h group; four 30-min exposures interspersed with 30 min of room light) showed the largest phase advance. This occurred despite not shifting bedtime earlier on treatment day 1 in the 2-h group as was done for the two other groups, which could have reduced the advance in the 2-h group. Reducing the duration of the four bright-light exposures from 30 to 15 min (1-h group) significantly reduced the phase advance, as did reducing the number of 30-min light exposures from four to one (0.5-h group). The 1-h and 0.5-h bright-light exposures, however, still produced about 70–75% of the phase advance as that produced by the 2-h exposure, even though the total duration of bright light was only 50% and 25% of the 2-h condition. Average phase advances in the 1-h and 0.5-h groups did not differ from one another, which showed that given 3 days of afternoon melatonin and a gradually advancing sleep schedule, the single 30-min bright-light exposure immediately after waking was just as effective as 1 h of intermittent light exposure spread across the first 3.25 h after waking.

These data suggest that the first morning light exposure likely contributes the most to the observed phase-advance shift. The single 30-min light exposure of the 0.5-h group produced about 75% of the phase shift of the 2-h group with four 30-min exposures, indicating that the subsequent exposures contributed less to the overall phase advance shift. This may also explain the similar phase advances seen in the 0.5-h group and the 1-h group; the first 15-min exposure contributed the most to the phase advance – about the same as the 30-min exposure – and the subsequent 15-min exposures of the 1-h group may have contributed less to the overall shift. These data mimic the findings of Chang and colleagues [80], who showed similar phase delay shifts (1.1 and 1.6 h) in response to 12 and 60 min of bright light (>6000 lux), respectively. The relative potency of the first exposure may be explained by studies showing that the beginning of the light exposure (the transition from dark to light) is the most effective in producing a phase shift compared to the subsequent hours of light exposure [62,81]. Alternatively or in addition, the first bright-light exposure of all groups was timed closer to the peak of the phase-advance region of the light PRC compared to the subsequent intermittent exposures. Data from the current study indicate that light treatment beginning at an earlier circadian time produced greater phase-advance shifts than light treatment beginning later (see Fig. 4). This pattern is consistent with previously published PRCs to bright light [21,82]. Of note, the overall magnitude of the phase shift was also driven by the exogenous melatonin timed close to the peak of the phase-advance region of the 0.5-mg melatonin PRC [25] over the three treatment days.

Three previous studies [38,60,61] compared the phase-shifting effects of long continuous bright-light exposures to intermittent bright-light patterns that spanned the same time interval and showed that intermittent light patterns can be very effective. Rimmer and colleagues [60] tested 3 days of bright-light exposures (up to ~10,000 lux) with four abruptly shifted sleep/dark episodes to produce phase advances. They showed that intermittent patterns spanning 5.8 h – one with 38- and 46-min exposures totaling 3.8 h, and another with 5.3-min exposures totaling 1.9 h – produced about 60–90% of the phase shift produced by 5.8 h of continuous bright light despite bright light being on for 33% and 66% of the time. Gronfier and colleagues [61] tested 1 day of bright light and two abruptly shifted sleep/dark episodes designed to produce phase delays. They showed that an intermittent pattern spanning 6.5 h with 15-min exposures totaling 1.5 h produced about 80% of the shift produced by 6.5 h of continuous bright light even though it was on for only 23% of the time. Using a similar protocol to the current study with 3 days of a 1-h/day advance of sleep/dark, we compared 3.5 h of continuous morning bright light (~5000 lux) to 2 h of intermittent light spanning the same 3.5-h time interval (four 30-min bright-light exposures interspersed with 30 min of room light) [38]. The intermittent pattern produced about 70% of the phase shift produced by 3.5 h of continuous bright light. In the current study, we compared two intermittent light patterns that spanned a similar time interval. The 15-min light exposure pattern produced 71% of the phase shift as the pattern with 30-min exposures even though the bright light was on for only 50% of the time. The low-cost-to-high-benefit ratio shown in all of these studies may be explained by animal data suggesting that the system is able to integrate these intermittent light stimuli over time [83]. More recently in humans, Zeitzer and colleagues [84,85] reported that brief 2-ms flashes of light in an otherwise dark room spaced over an hour can delay circadian rhythms.

Previous studies compared different durations of continuous bright-light exposures, and showed that longer durations produced larger phase shifts [49,80,86]. Previously in our laboratory, we compared daily bright light (~5000 lux) with durations of 3 or 6 h along with an abrupt 12-h shift of sleep/dark for 8 days [49]. The phase shift averaged over the last 4 days was 8.1 h for the 3-h duration and 9.4 h for the 6-h duration. A second study [86] tested three bright-light durations (1, 2, and 3 h) with different light intensities (2000, 4000, and 8000 lux). Subjects were awakened for a single bright-light exposure in the middle of their sleep period before the temperature minimum to produce phase delays. When averaged over the three light intensities, the phase shifts were 0.4, 1.1, and 1.7 h for the 1-, 2-, and 3-h durations, respectively. Another study [80] measured phase shifts to bright-light exposures (>6000 lux) in a protocol that included one day with bright light and two abruptly shifted sleep/dark episodes designed to produce phase delays. Bright-light durations of 0.2, 1.0, 2.5, 4.0, or 6.5 h produced phase shifts of 1.1, 1.6, 2.3, 2.7, and 3.1 h. From these data, they constructed a duration response curve, which was approximately linear between 0.2 and 2.5 h and then appeared to level off (saturate). Taken together, these studies suggest that increasing the duration of continuous bright light by more than about 3 h results in minimal gains to phase-shift the circadian system. In the current study, the intermittent light pattern with the longest duration (2 h) produced the largest phase shifts. It is possible that adding more light exposures would increase the phase shift; however, increasing the time may reduce the feasibility of the bright-light treatment.

Thus far, we have discussed studies that compared different durations and patterns of bright light; however, the current study also included exogenous melatonin to phase-shift circadian rhythms. Outside of our laboratory, we know of two studies that combined afternoon melatonin and morning light to produce a phase advance in circadian rhythms [87,88]. Paul and colleagues [87] administered 3 mg sustained-release melatonin at 4:00 pm, after which participants went to bed (approximately 8 h before their usual bedtime). Participants were then awakened about 2.5 h before their usual wake time and were exposed to green light for 1 h. This single day of afternoon melatonin, morning light, and an abrupt advance of the sleep schedule produced a phase advance of 1.0 h. Burke and colleagues [88] administered 5 mg of melatonin 5.75 h before the habitual bedtime, and 3 h of bright light (~3000 lux) starting 1 h before the habitual wake time. This single day of afternoon melatonin and morning light produced a phase advance of 1.3 h. In the current study, 0.5 mg of afternoon melatonin and three different morning light patterns applied over 3 days produced descriptively larger phase advances than the two studies described above, especially for the 2-h group (2.4 h). Similarly, 3 mg of afternoon melatonin combined with 2 h of bright intermittent light over 3 days also produced descriptively larger phase-advance shifts (2.6 h) [41] than these previous studies. These larger phase shifts from our laboratory are expected because the treatment was repeated over 3 days.

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Despite different protocols, different melatonin doses, and different types of morning light among previous studies, the phase-advancing effect of morning light alone and afternoon melatonin alone are roughly similar and when combined they are roughly additive. In our gradually advancing sleep/dark protocol, we have shown that 3 mg of afternoon melatonin alone produced a phase advance of 1.3 h [37], morning light alone (30 min × 4 exposures) produced phase advances of 1.5 h [38] and 1.7 h [41], and the combination produced a phase advance of 2.6 h [41]. Paul and colleagues [87] also show this additive pattern; afternoon melatonin produced a phase advance of 0.7 h, morning light advanced rhythms by 0.3 h, and the combination advanced rhythms by 1.0 h. Finally, in the study of Burke and colleagues [88], afternoon melatonin alone, morning light alone, and the combination produced phase advances of 0.6, 0.7, and 1.1 h, respectively. Therefore, all of these studies show an additive effect of melatonin and bright light, and all of these studies illustrate that the largest phase advances are produced with the combination of melatonin and light.

The largest phase advance in the current study was seen in the 2-h group and averaged 2.4 h, but the sleep/wake schedule advanced by 3 h by the last treatment day. Thus, by the end of the protocol, there was a small degree of circadian misalignment because the advance in the circadian system was not enough to keep up with the advance in the sleep/wake schedule. In the other two groups with less morning bright-light exposure, the phase advances were smaller (1.7 and 1.8 h); thus, there was a slightly greater amount of circadian misalignment by the end of treatment in these groups compared to the 2-h group. The degree of circadian misalignment in each group by the end of the protocol can be estimated by comparing the interval between the DLMO and bedtime before and after the phase-advancing treatment (ie, baseline DLMO to baseline bedtime vs. final DLMO to treatment day 3 bedtime in Table 1). The average difference was 0.5 h in the 2-h group, 1.3 h in the 1-h group, and 1.1 h in the 0.5-h group. Although there was a small degree of misalignment between circadian rhythms and sleep timing, the total sleep time did not differ and sleepiness ratings were not worse at the end of the protocol compared to baseline for any of the groups. Jet lag scores from the Columbia scale were slightly higher than baseline near the end of the protocol, with no differences among the three groups. These elevated scores likely reflect the cumulative amount of circadian misalignment by the last treatment day in all groups. A previous study from our laboratory [38] tested morning bright light without melatonin (continuous vs. intermittent bright-light exposure over 3.5 h) versus dim light in the same phase-advancing protocol as the current study. On average, continuous bright light advanced rhythms by 2.1 h, intermittent bright light advanced rhythms by 1.5 h, and dim light phase-advanced rhythms by 0.6 h. Again, none of these groups were completely aligned with the 3-h shifted sleep schedule by the end of treatment; however, smaller phase advances (i.e., greater circadian misalignment) were associated with more jet lag symptoms.

In addition to circadian misalignment, the slightly elevated Columbia Scale jet lag scores in the current study might also be due to the acute side effect of melatonin (sleepiness), especially as the questionnaire was filled out a few hours after ingesting the pill. Our previous studies using evening melatonin showed an increase in subjective sleepiness in the hours after taking 3.0 mg of melatonin [37,41], but not after taking 0.5 mg of melatonin (see fig. 6 in Ref. [41]). The lower dose of melatonin (0.5 mg) was used in the current study to reduce the risk of sleepiness. Therefore, we think it unlikely that residual or acute effects of melatonin are contributing significantly to these slightly elevated jet lag symptoms. Generally, this method for advancing circadian rhythms produced only a small degree of circadian misalignment and jet-lag-type symptoms. If our treatment protocol was continued for >3 days, however, it is possible that the circadian system would lag behind the sleep schedule even more, producing a greater degree of circadian misalignment and eventually jet lag symptoms, including sleep difficulties.

There are several ways to reduce the potential for circadian misalignment when using our method for advancing circadian rhythms. First, we recommend using the longest practical duration of continuous bright light as early in the morning after waking as possible as this study and the others reviewed above show larger phase shifts with more hours of bright light and larger advances with earlier morning light. We also recommend using a light box as large as possible to cover as much of the visual field as possible [89] and seeking outdoor sunlight exposure when it is daytime rather than using a light box [11]. Another way to reduce circadian misalignment while advancing the circadian system is to reduce the amount of time that sleep/dark is shifted each day; for example, advancing sleep/dark times by 30 or 45 min/day instead of 1 h may keep the sleep schedule more aligned with circadian rhythms. Reducing the daily sleep/dark shift to <1 h, however, still needs to be tested. Another way to reduce circadian misalignment with our method is to start using the melatonin and bright light a day or two before the sleep/wake schedule is advanced (see figs. 30-5 and 30-7 in Revell and Eastman [11]) rather than waiting until the first day that sleep/dark is advanced. Finally, for cases in which bedtime advances to a time when there is daylight, exposure to outdoor light in the hours before bedtime should be avoided as this could delay rhythms. Dimming indoor lights or even wearing sunglasses in the few hours before bedtime could also reduce this risk, as data suggest that even normal indoor lighting in the evening can delay rhythms [90]. Creating a dark environment to sleep (eg, with blackout shades or dark material over windows) is also recommended because the advance of the sleep/dark period removes the light from the phase delay portion of the PRC and thus facilitates the desired phase advance.

In real-life settings, the recommendation of which melatonin dose to use depends on the individual's circumstances. For coping with an abrupt advance of sleep after it occurs, for example, after flying east across several time zones with no preflight adjustment, taking sustained-release melatonin before the advanced bedtime in the new time zone, as simulated by Paul and colleagues [87], is appropriate. Our method of a gradual advance of sleep/dark with afternoon melatonin and morning bright light is designed to be used a few days before the earlier sleep schedule is required (eg, before eastward jet travel, before early-morning shift work, or before the transition back to early school start times after a vacation) and will not produce the extreme circadian misalignment that comes from a large abrupt shift of sleep. Exogenous melatonin is taken several hours before bedtime when using this method. We [37,41] and others [91–94] have found that high doses of afternoon melatonin (eg, 2–10 mg) will likely produce unwanted evening sleepiness. Thus, for those who are sensitive to the sleepiness produced by melatonin, we recommend the 0.5-mg dose, which we showed did not produce more sleepiness than placebo [41]. Our melatonin PRC studies [25] show that the average magnitude of the phase shifts is similar between a 0.5- and 3-mg dose; however, the 3-mg dose is more likely to produce reliable phase shifts compared to the 0.5-mg dose. Therefore, we recommend the 3-mg dose if possible, especially if there are no evening activities that require vigilance, such as driving.

The current study is limited by studying only healthy young adult participants. Future studies may consider testing these phase-advancing strategies on older adults or patients with circadian-based sleep disorders, such as DSPD. The scope of the study was limited to comparing three morning bright-light patterns with one melatonin dose. A number of light patterns and melatonin doses are possible, however, and some could be more effective than, yet as feasible as, a single 30-min exposure (eg, one 30-min exposure with 3.0 mg of melatonin). Questioning participants about the

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feasibility of such treatments at home is also missing, and we suggest collecting such feasibility data in future work.

In summary, the current study tested three different morning bright-light patterns combined with a low dose of afternoon melatonin and a gradual advance of sleep/dark over 3 days to advance circadian rhythms. Such a strategy could be used to help night owls or people with DSPD, to help people adapt to an early work or school schedule, to help a shift worker who has to work early-morning shifts, or help travelers to reduce or prevent jet lag. The 2-h (30 min × 4) morning bright-light exposure produced the largest phase advance; however, one 30-min bright-light exposure immediately upon waking each day is effective and takes a quarter of the time.

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Conflict of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.12.004.

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